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Review

Evaluation and management of extrahepatic manifestations of nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is a multisystemic disease and a rapidly growing cause of chronic liver disease in children and adults worldwide. Diagnosis and management of extrahepatic manifestations of NAFLD, including cardiovascular disease (CVD), type 2 diabetes mellitus, metabolic syndrome, chronic kidney disease, obstructive sleep apnea, polycystic ovarian syndrome, hypothyroidism, psoriasis, and extrahepatic malignancy are crucial for the treatment of patients with NAFLD. The leading cause of death in NAFLD is primarily from CVD, followed by liver-related mortality, extrahepatic cancer, liver cancer, and diabetes-related mortality. Therefore, clinicians need to identify high-risk patients earlier in the disease course and be aware of the extrahepatic manifestations of NAFLD to improve liver disease outcomes. In this review, we focus on the monitoring and management of the extrahepatic manifestations of NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease characterized by triglyceride deposits in hepatocytes without secondary causes of liver disease, including significant alcohol consumption.¹ NAFLD represents a broad clinical spectrum of diseases ranging from simple hepatic steatosis through steatosis with inflammation and hepatocyte degeneration (nonalcoholic steatohepatitis [NASH]) that can lead to advanced fibrosis, cirrhosis, and hepatocellular carcinoma.¹ NAFLD is a sig-

nificant health problem worldwide, and its burden is expected to rise. A meta-analysis demonstrated that the prevalence of NAFLD is 25.2% worldwide, with the highest in South America and the Middle East (30.5% and 31.8%, respectively) and lowest in Africa (13.5%).² Despite the high prevalence of NAFLD in the general population, only a minority of patients with NAFLD will progress to NASH with advanced fibrosis or develop liver-related complications.³

Recently, an international consensus group suggested considering a new acronym, metabolic (dysfunction) associated fatty liver

Abbreviations:

AASLD, American Association for the Study of the Liver Disease; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; EASL, European Association for the Study of the Liver; GLP-1, glucagon-like peptide 1; HR, hazard ratio; IRR, incidence rate ratio; LDL, low-density lipoprotein; MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; PIVENS, Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH; RAS, renin-angiotensin system; SGLT-2, sodium-glucose cotransporter type-2; TNF, tumor necrosis factor; UDCA, ursodeoxycholic acid

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disease (MAFLD), to more accurately reflect the current knowledge of the disease pathophysiology and help with risk stratification and management due to the heterogeneity of clinical presentation of fatty liver disease.⁴ Even though MAFLD may more appropriately reflect the relevant risk factors for the disease better than NAFLD, the term remains vague. Prior to a name change, an improved understanding of the pathogenesis, natural history, and treatment of NAFLD is needed.⁵ NAFLD is a multisystem disease with effects,⁶ thus physicians should be aware of the manifestations of NAFLD beyond the liver, such as cardiovascular disease (CVD), with the goal of early recognition and management.^{7,8}

Previous studies have shown that the most common cause of death associated with NAFLD is CVD, independent of other metabolic comorbidities, followed by extrahepatic cancer and liver-related complications.^{1,9,10} A recent USA study reported that the cause of death in NAFLD was more likely to be CVD (about 20%), whereas mortalities for extrahepatic cancer and diabetes compared with CVD showed a more pronounced increase annually during the recent decade.¹¹ In this review, we focus on recognizing and managing the extrahepatic manifestations of NAFLD.

CVD

CVD is the major cause of death among individuals with NAFLD.¹² Risk factors for NAFLD are similar to those for CVD, including insulin resistance, type 2 diabetes, male sex, hypertension, dyslipidemia, metabolic syndrome, and obesity.^{12,13} NAFLD is associated with an increased risk of incident CVD independent of traditional risk factors and components of metabolic syndrome.¹² A recent meta-analysis showed that NAFLD is associated with a higher risk of fatal and non-fatal cardiovascular events, such as stroke, angina, myocardial infarction, or coronary revascularization, compared to those without NAFLD.¹⁴ It should be noted that patients with NAFLD who are not overweight also have an increased risk of CVD compared with those without NAFLD who are not overweight.¹⁵ In addition, the risk of CVD in non-overweight NAFLD (hazard ratio [HR], 10.4; 95% confidence interval [CI], 2.61–44.0) was higher than those who are overweight in the setting of NAFLD (HR, 3.14; 95% CI, 0.84–13.2).¹⁵ Further studies are needed to confirm this finding.

The pathophysiologic mechanisms that link NAFLD and CVD, including pro-inflammatory mediators, altered coagulation and fibrinolysis, shared metabolic CVD risk factors, have been summarized in the previous literature.^{7,16} Moreover, evidence suggests

that NAFLD is associated with an increased risk of premature atherosclerosis.^{12,17,18} Thus, aggressive screening for metabolic and CVD risk factors as well as risk factor modification are essential strategies to reduce the risk of CVD mortality.¹⁹

The European Association for the Study of the Liver (EASL) and American Association for the Study of the Liver Disease (AASLD) guidelines recommend screening for metabolic risk factors in patients with NAFLD; however, at this time there is no role for screening asymptomatic individuals with NAFLD for CVD.^{1,20} An algorithm to screen and manage metabolic risk factors, including obesity, diabetes, dyslipidemia, and hypertension, in patients with NAFLD, has been proposed by Wong and Lim.¹⁹ Currently, there are nonpharmacological, pharmacological, and surgical management strategies with the potential to reduce CVD risk in individuals with NAFLD.

Nonpharmacological strategy

Nonpharmacological management or lifestyle modifications, including weight loss, increased physical activity, and diet control, should be recommended to every patient with NAFLD. Lifestyle modifications, especially in the early stages, are associated with reduced CVD risk as well as improved results of blood tests for liver function, hepatic steatosis, liver histology, and fibrosis in patients with NAFLD.¹ Greater than 5% weight loss is associated with an improvement in hepatic steatosis and reduction in NAFLD activity score. In contrast, weight loss of greater than 10% is also associated with fibrosis regression.^{1,20,21} Despite the benefits of weight loss, few can achieve significant weight loss with lifestyle interventions. Only 50% of patients in an intensive lifestyle intervention program were able to achieve greater than 7% weight loss at 12-month follow-up, and there were concerns regarding the sustainability of the weight loss.²¹

A calorie-restricted diet for more than 1 year has been shown to significantly lower atherosclerosis risk in NAFLD.^{22,23} In addition, caloric restriction has been shown to reduce liver fat content.²⁴ Daily reduction by 500–1,000 kcal has been recommended for patients with NAFLD by several guidelines.^{1,20,25} Moreover, several studies recommend restricting processed food, red meat, saturated fat, as well as beverages containing high fructose and artificial sweeteners.^{1,20,26–28} An epidemiological study comprised of an ethnically diverse population showed that decreasing consumption of red and processed meat, cholesterol, and poultry and increasing fiber consumption may reduce the risk of NAFLD and NAFLD-related cirrhosis.²⁹ Recently, one study showed that a low

carbohydrate Mediterranean diet decreases liver fat more than a low-fat diet in NAFLD.³⁰ A large randomized controlled trial demonstrated a decreased incidence of CVD events in individuals consuming a Mediterranean diet based on extra-virgin olive oil and nuts compared to consuming a reduced-fat diet.³¹ A recent systematic review and meta-analysis showed that in patients with NAFLD, adherence to the Mediterranean diet reduced serum triglyceride, total cholesterol, body weight, and insulin resistance, all of which are closely tied to cardiovascular health.³² EASL and AASLD guidelines both agree that patients with NAFLD should avoid substantial amounts of alcohol consumption,^{1,20} less than 30 g/day in men and 20 g/day in women.²⁰ Alcohol abstinence is highly suggested for those with NASH-cirrhosis to reduce the risk of hepatocellular carcinoma.²⁰ Interestingly, coffee consumption can be considered as a potential lifestyle modification based on the EASL guidelines; this modification is suggested given a recent systematic review that demonstrated that coffee consumption is inversely related to the severity of steatohepatitis.^{20,33} Further work has shown that more than 3 cups of coffee per day is associated with a lower risk of CVD and risk of death post-myocardial infarction.^{20,34-36}

Inadequate physical activity or sedentary lifestyle is a risk factor associated with NAFLD and CVD.³⁷⁻³⁹ A recent US population-based study showed that the prevalence of meeting the physical activity guidelines (≥ 150 min/week) was markedly higher in subjects without NAFLD than those with NAFLD, which was mostly attributable to the higher prevalence of leisure-time physical activity in those without NAFLD.³⁷ Physical activity is a proven therapeutic strategy to improve liver fat content, insulin resistance, and decrease the risk of CVD.⁴⁰⁻⁴² In a systemic review and meta-analysis, exercise interventions were shown to be associated with a reduction in liver fat in spite of minimal to no weight loss.⁴³ In a recent longitudinal USA population-based study, increasing total physical activity was associated with a lower overall and cardiovascular mortality in individuals with NAFLD.⁴⁴ In patients with NAFLD, the EASL guideline recommends moderate-intensity aerobic physical activity in 3–5 sessions for a total of 150–200 minutes per week.²⁰ Although various types of physical activity have demonstrated a significant inverse association with advanced fibrosis in the USA population study, the ability to physical activity alone to improve liver fibrosis needs further study.^{1,37,45} Therefore, current AASLD and EASL guidelines recommend a combination of a hypocaloric diet with moderate-intensity physical activity to achieve and maintain weight loss over time.^{1,20}

Pharmacological strategy

Several pharmacological therapies may have cardioprotective effects in individuals with NAFLD, including anti-diabetic medications, lipid-lowering medication, antioxidants, semi-synthetic bile acid analogs (obeticholic acid), aspirin, and renin-angiotensin system (RAS) inhibitors.^{1,20,46} Table 1 summarizes the potential effects of each medication on improvement in NASH, hepatic fibrosis, and reduction of the CVD risk.

Anti-diabetic medications which may have the potential cardioprotective effects in patients with NAFLD include metformin, thiazolidinedione, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter type-2 (SGLT-2) inhibitors.^{1,20,46,47} Recent studies reported that metformin use was associated with lower CVD and CVD-related mortality in patients with and without diabetes.^{48,49} However, metformin has not been shown to improve NASH or liver fibrosis.^{50,51} Therefore, current guidelines do not recommend metformin for the specific treatment of NASH.^{50,51}

Thiazolidinediones, such as pioglitazone, are peroxisome proliferator-activated receptor agonists with insulin-sensitizing effects that have been shown to decrease the progression of liver injury and fibrosis in patients with biopsy-proven NASH irrespective of diabetes.^{1,52-54} The pioglitazone versus vitamin E versus placebo for the treatment of nondiabetic patients with NASH (PIVENS) trial demonstrated an improvement in hepatic steatosis and lobular inflammation without improvement in fibrosis scores in nondiabetic patients.⁵⁴ Cusi et al.⁵³ determined that long-term use pioglitazone, along with a hypocaloric diet, led to an improvement in metabolic and liver histology among patients with NASH and prediabetes or type 2 diabetes. In addition, a recent meta-analysis reported that pioglitazone was associated with a reduction of a major CVD event in patients with insulin resistance, prediabetes, and type 2 diabetes.⁵⁵ However, it should be noted in a systemic review and meta-analysis that pioglitazone was associated with an increased risk of heart failure, weight gain, edema, and bone fractures.⁵⁵ These findings of reduced major CVD events, but increased risk of heart failure with pioglitazone were corroborated by a recent large umbrella review.⁵⁶ Thus, the risks and benefits of thiazolidinediones should be discussed with the patients before starting the medication.

GLP-1 agonists, such as liraglutide, have been studied in patients with NAFLD and NASH.^{57,58} A randomized controlled trial (phase 2) showed histological improvement and reduced fibrosis progression as well as weight loss in patients with NASH who re-

Table 1. Summary of potential interventions for nonalcoholic fatty liver disease

Intervention	Improvement of nonalcoholic steatohepatitis	Improvement of hepatic fibrosis	Cardioprotective effects
Lifestyle modification			
Weight loss	✓	✓	✓
Dietary modification (calorie restriction, Mediterranean diet, low carbohydrate diet)	✓	✓	✓
Physical activity	✓	✓	✓
Pharmacological treatment			
Metformin	No benefit	No benefit	Potential benefit
Thiazolidinedione	✓	Inconclusive	Potential benefit but increase risk of heart failure
GLP-1 receptor agonists	✓	✓	Potential benefit
SGLT-2 inhibitor	✓	✓	Potential benefit
DPP-4 inhibitor	Inconclusive	No benefit	No benefit
Statins	No benefit	Inconclusive	✓
Omega-3-fatty acids	No benefit	No benefit	No benefit
Vitamin E	✓	No benefit	No benefit
Ursodeoxycholic acid	✓	Inconclusive	No benefit
Obeticholic acid	✓	✓	Unknown, possible increase risk of CVD due to increase LDL-cholesterol
Aspirin	Unknown	Inconclusive	✓
Renin-angiotensin inhibitors	Unknown	✓	✓
Surgical management			
Bariatric surgery	✓	✓	✓

GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter type-2; DPP-4, dipeptidyl peptidase 4; CVD, cardiovascular disease; LDL, low-density lipoprotein.

ceived liraglutide 1.8 mg/day for 48 weeks compared to placebo.⁵⁸ A subsequent study reported that patients with uncontrolled type 2 diabetes who received liraglutide 1.2 mg/day for 6 months had significantly reduced liver fat content.⁵⁹ Moreover, liraglutide has been demonstrated to be associated with a decreased risk of CVD and cardiovascular mortality in type 2 diabetes.^{60,61} Although the current AASLD guideline suggests that it is premature to consider GLP-1 agonists for the treatment of NASH or NAFLD,¹ emerging evidence has suggested a cardioprotective effect of liraglutide in type 2 diabetes.^{60,61} Therefore, GLP-1 agonists may be considered for the treatment of diabetes in patients with NAFLD given its associated cardioprotective effect.

SGLT-2 inhibitors represent another pharmacologic option. A recent meta-analysis showed that SGLT-2 inhibitors are associated with the improvement of results of blood tests for liver function, hepatic fat content, and hepatic fibrosis in patients with type 2

diabetes with NAFLD.⁶² In addition, studies also supported the cardioprotective effect of SGLT-2 inhibitors in patients with type 2 diabetes.^{63,64} Current guidelines did not provide any recommendations for SGLT-2 inhibitors use for the treatment of NASH or NAFLD.^{1,20,25} Further studies are warranted to investigate the cardioprotective effect of long-term SGLT-2 inhibitors use in patients with NAFLD. It should be noted that SGLT-2 inhibitors are associated with the genitourinary tract infections, and less frequent adverse events, such as diarrhea, acute kidney injury, and bone fractures.⁶⁵

Dipeptidyl peptidase 4 (DPP-4) inhibitors, such as sitagliptin, were evaluated among patients with NAFLD. Several studies demonstrated that patients with type 2 diabetes and NASH who received sitagliptin showed improvement in results of blood tests for liver function, parameters in diabetes, liver fat content, and liver histology.^{66,67} However, there have been some conflicting re-

sults on the impact of DPP-4 inhibitors use on liver histology. In a small placebo-controlled trial in 12 patients with biopsy-proven NASH, there was no improvement of hepatic fibrosis or liver histology after 24 weeks of sitagliptin therapy.⁶⁸ However, a subsequent randomized controlled trial showed that one year of sitagliptin 100 mg daily in patients with NASH led to an improvement in liver histology and hepatocyte ballooning, but without any change in fibrosis scores; these improvements were noted irrespective of diabetes.⁶⁹ Studies suggested that sitagliptin could be safely used in type 2 diabetes and not associated with an increased risk of major adverse CVD events nor was it associated improved CVD outcomes.^{70,71} In a comparative cohort study, initiation of SGLT-2 inhibitors was associated with lower risks of heart failure, myocardial infarction, and stroke compared to initiation of DPP-4 inhibitors.⁷² Current guidelines did not discuss the role of DPP-4 inhibitors in patients with NASH or NAFLD, but given the associated cardioprotective effect with other agents, such as SGLT-2 inhibitors, for the treatment of diabetes, clinicians should consider favoring anti-diabetic agents with associated cardioprotective effects in patients with NAFLD.

Despite the fact that statins are approved for primary prevention of CVD in high-risk patients given the well-known protective effects against CVD, there is insufficient evidence to recommend statin use for the treatment of liver disease in individuals with NAFLD.^{73,74} Despite inconsistent results regarding improvement in liver histology and liver chemistries in patients with NASH,⁷⁵⁻⁷⁹ statins use has been demonstrated to improve surrogate markers of serum lipids for CVD prevention.⁸⁰ Statins have been known to be safe for the treatment of dyslipidemia in patients with NAFLD or NASH but should be avoided in patients with decompensated cirrhosis due to NASH.^{1,20,81} At present, given that the high risk of CVD mortality in patients with NASH or NAFLD, the benefits of statins use for the treatment of dyslipidemia outweigh the risk for adverse effects from statins and should be considered in the treatment of dyslipidemia.^{1,20}

Omega-3 fatty acids are approved for the treatment of hypertriglyceridemia but are not currently recommended for treatment of NAFLD or NASH^{1,20,82,83} or for primary prevention of CVD.^{84,85}

AASLD guidelines recommend considering vitamin E 800 IU per day for nondiabetic biopsy-proven NASH without cirrhosis after discussing the risk and benefit of the medication based on the PIVENS trial.^{1,54} At present, there is no strong evidence evaluating the cardioprotective effect of vitamin E in patients with NAFLD. In the general population, there is no evidence for reduced CVD risk associated with vitamin E supplementation.^{86,87} Ursodeoxycholic

acid (UDCA) was not recommended by the current guideline for the treatment of NASH since several large multicenter trials showed no histologic benefit over placebo.^{1,20,88} Similar to vitamin E, further studies are warranted to investigate the possible cardio-protective effect of UDCA specifically in patients with NAFLD.

Obeticholic acid is a promising agent for the treatment of NASH. A recent multicenter randomized controlled phase 3 trial reported that patients with NASH who received obeticholic acid 25 mg daily had significant improvement in hepatic fibrosis, histology, and key components of disease activity in NASH.⁸⁹ It should be noted that obeticholic acid is associated with adverse events, including dose-related pruritus, elevated total cholesterol, and low-density lipoprotein (LDL) cholesterol level, some of which are postulated to be transient given elevated LDL cholesterol levels at 1 month, then approached baseline at 18 months. However, further studies are warranted to determine the real-world impact of obeticholic acid on the risk of CVD, especially given the undesirable effect of obeticholic acid on the lipid profile in patients with NAFLD.

Currently, there are no randomized controlled trials regarding the cardioprotective effect of aspirin, especially in patients with NASH or NAFLD. Observational studies with biopsy-proven NAFLD have shown that daily aspirin use was associated with less severe histologic features of NASH and fibrosis, and daily aspirin users had a significantly lower risk for developing advanced fibrosis, which appeared to be duration dependent.^{90,91} Current guidelines do not provide any recommendations regarding daily aspirin use in patients with NAFLD. Further longitudinal studies are required to determine the cardioprotective effect and hepatoprotective effect of aspirin in patients with NASH.

A meta-analysis study of four trials of 210 patients with advanced fibrosis due to multiple etiologies showed that RAS inhibitor use is associated with a reduction in hepatic fibrosis scores and area of fibrosis; however, high-quality large randomized controlled trials are required to confirm these findings.⁹² Current AASLD guidance does not discuss the role of RAS inhibitors for the treatment of NAFLD. Further studies are needed to investigate the effect of RAS inhibitors on liver histology and fibrosis as well as CVD risk among patients with NAFLD.

Surgical management strategy

Bariatric surgery is an option for patients with NASH who remain unresponsive to lifestyle and pharmacological management.^{1,93,94} Many observational studies have shown an improve-

ment in histology and fibrosis in patients with NASH following bariatric surgery.^{95–97} A prospective study of 109 patients with NASH found that hepatic fibrosis improved in 33% of patients, and 85% of patients had NASH resolution at a 1-year follow-up liver biopsy.⁹⁷ A meta-analysis showed that bariatric surgery results in the resolution of steatosis (66%), lobular inflammation (50%), and fibrosis (40%) in patients with NAFLD.⁹³ Previous studies have shown a lower risk of CVD events and incident heart failure in patients who underwent bariatric surgery.^{98,99} Further studies are needed to investigate whether bariatric surgery has a potential cardioprotective effect in the setting of NAFLD or NASH.

In summary, patients with NASH or NAFLD should be screened for risk factors associated with CVD, such as abdominal obesity, diabetes, dyslipidemia, metabolic syndrome, and hypertension, and initiate early treatment to prevent CVD complications. Early lifestyle modifications (7–10% of body weight loss, dietary changes, and increasing physical activity) remain the cornerstone for primary and secondary prevention of CVD. Monitoring fasting blood glucose, hemoglobin A1c, blood pressure, and lipid profiles in patients with NAFLD has been proposed in previous literature.^{7,100} Based on the current AASLD guidelines, statins can be used for the treatment of dyslipidemia in patients with NAFLD and NASH, but there is no approved medication for the treatment of NASH to prevent CVD.^{1,20} In terms of surgical interventions, bariatric surgery has been shown to improve liver histology and fibrosis in NASH.⁹³ However, long-term outcome studies are needed to investigate the impact of bariatric surgery on CVD risk reduc-

tion among patients with NAFLD or NASH.

TYPE 2 DIABETES MELLITUS

NAFLD has been shown to be an independent risk factor for type 2 diabetes mellitus. NAFLD and type 2 diabetes share several pathophysiologic backgrounds, including obesity, insulin resistance, and metabolic syndrome.^{1,6} A study evaluating the association between NASH and insulin resistance showed that most patients with NASH have insulin resistance and that the association between NASH and insulin resistance is independent of obesity.¹⁰¹ A recent meta-analysis demonstrated the high global prevalence of NAFLD (55%; 95% CI, 47.3–63.7%) and NASH (37.3%; 95% CI, 24.7–50.0%) in patients with type 2 diabetes.¹⁰² Advanced fibrosis in patients with NAFLD and type 2 diabetes is approximately 17% (95% CI, 7.2–34.8%).¹⁰² In addition, a meta-analysis demonstrated the increased incidence of type 2 diabetes in patients with NAFLD with a pooled HR of 2.22 (95% CI, 1.84–2.60).¹⁰³ However, it should be noted that NAFLD and type 2 diabetes have a bidirectional relationship and can develop simultaneously, which can confound the prevalence of NAFLD in type 2 diabetes.¹ This emphasizes the importance of increased awareness of the association between NAFLD and type 2 diabetes to all important stakeholders, including primary care physicians, specialists, and policymakers. The current AASLD guidance states that noninvasive fibrosis imaging, such as vibration-controlled transient elastogra-

Table 2. Summary of potential treatment strategy for extrahepatic manifestations in nonalcoholic fatty liver disease

Extrahepatic manifestations	Behavioral intervention (weight loss, diet restriction, physical activity)	Pharmacological treatment	Bariatric surgery
Cardiovascular disease	√	Possible aspirin, statins, RAS inhibitor	Potential benefit
Type 2 diabetes mellitus	√	Diabetic medication (metformin, thiazolidinedione, GLP-1 agonist, SGLT-2 inhibitor, DPP-4 inhibitor), aspirin, statins	√
Metabolic syndrome	√	Possible statins	No indication
Hypertension	√	Possible RAS inhibitors	No indication
Chronic kidney disease	√	Possible RAS inhibitors	No indication
Extrahepatic malignancy	√	No indication	No indication
Obstructive sleep apnea	√	No indication	No indication
Hypothyroidism	√	Thyroid replacement therapy	No indication
Polycystic ovarian syndrome	√	Metformin	No indication
Psoriasis	√	Possible TNF-inhibitor (etanercept)	No indication

RAS, renin-angiotensin system; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter type-2; DPP-4, dipeptidyl peptidase 4; TNF, tumor necrosis factor.

phy, can be used to stratify patients with NAFLD as low or high risk for advanced fibrosis.¹ At this time, routine screening for NAFLD in patients with type 2 diabetes is not advised due to the uncertainty of diagnostic tests and treatment options and the lack of evidence to support long-term benefits with cost-effective screening.¹ However, given the increased risk of type 2 diabetes in patients with NAFLD, annual screening for type 2 diabetes with glycosylated hemoglobin or oral glucose tolerance test was proposed in a recent study.¹⁰⁴ A study suggests that NAFLD screening in individuals with type 2 diabetes may be potentially valuable and cost-effective.¹⁰⁵ The treatment strategy for type 2 diabetes in patients with NAFLD is summarized in Table 2.

CHRONIC KIDNEY DISEASE (CKD)

Several studies demonstrated that NAFLD was independently associated with the risk of CKD regardless of cardiorenal risk factors status such as obesity, hypertension, or type 2 diabetes.¹⁰⁶⁻¹¹² In a systematic review and meta-analysis, the severity of NAFLD was associated with an increased risk and severity of CKD, which remained significant in diabetic and nondiabetic populations as well as in studies that adjusted for typical CKD risk factors.¹¹³ Moreover, a recent meta-analysis demonstrated a significantly increased risk of albuminuria in patients with NAFLD, which can predispose to CKD.¹¹⁴ A recent review article summarized potential mechanisms between NAFLD and CKD, such as shared risk factors (type 2 diabetes, metabolic syndrome, obesity, hypertension), perturbation of the intestinal microbiota, prothrombotic state, platelet activation, and increased uric acid levels.¹¹⁰ The current guidelines did not address the management of CKD in patients with NAFLD or NASH.^{1,20} Some experts have proposed a potential screening strategy, which includes yearly urine microalbumin, albumin/creatinine ratio, and glomerular filtration rates in patients with NAFLD or NASH for early detection of CKD especially those with comorbid conditions, such as type 2 diabetes and obesity; however, there is insufficient evidence to establish formal guidelines for screening CKD in patients with NAFLD.¹⁰⁰

EXTRAHEPATIC MALIGNANCY

Extrahepatic malignancy-related mortality has been shown to be among the top three common causes of death in patients with NAFLD or NASH.^{10,115} A recent study based on the USA national

mortality database showed that hematologic and solid cancer-related mortality among subjects with NAFLD had significantly increased in the recent decade.¹¹ A recent longitudinal cohort study demonstrated that NAFLD was associated with a higher risk of extrahepatic malignancy including uterine cancer (incidence rate ratio [IRR], 2.3; 95% CI, 1.4–4.1), gastric cancer (IRR, 1.8; 95% CI, 1.3–4.1), pancreatic cancer (IRR, 2.0; 95% CI, 1.2–3.3), and colon cancer (IRR, 1.8; 95% CI, 1.1–2.8) after 21 years of follow up.¹¹⁶ NAFLD was associated with an estimated 2-fold increased risk of malignancy, especially within the liver, gastrointestinal tract, and uterus.¹¹⁶ In a systematic review and meta-analysis, NAFLD was associated with various extrahepatic malignancies, colorectal cancer (pooled odds ratio [OR], 1.72; 95% CI, 1.40–2.11), colorectal adenoma (pooled OR, 1.37; 95% CI, 1.29–1.46), intrahepatic cholangiocarcinoma (pooled OR, 2.46; 95% CI, 1.77–3.44), extrahepatic cholangiocarcinoma (pooled OR, 2.24; 95% CI, 1.58–3.17), and gastric cancer (pooled OR, 1.74; 95% CI, 1.03–2.95).¹¹⁷ Given this data, clinicians should be aware of the concern for increased risk of extrahepatic malignancy in patients with NAFLD. Physicians should emphasize that patients with NAFLD are up to date with their cancer surveillance, including colon cancer and breast cancer surveillance based on current guidelines. Patients should be counseled regarding behaviors that may be associated with an increased cancer risk, such as heavy alcohol consumption and smoking.

OBSTRUCTIVE SLEEP APNEA (OSA)

OSA has been shown to be correlated with the presence of NAFLD and severity of NAFLD, including lobular inflammation, ballooning degeneration, and fibrosis.¹¹⁸⁻¹²⁰ A recent study demonstrated an increased prevalence of NAFLD in patients with OSA, even in the absence of obesity or metabolic syndrome.¹²⁰ The data on the association between OSA and fibrosis are mixed. The degree of hypoxic burden due to OSA is associated with increased fibrosis.^{118,121,122} However, in a cohort of nearly 1,300 subjects with suspected OSA, the associated risk of hepatic fibrosis was not significant in the multivariate model.¹²³ There are some evidences that the treatment of OSA with continuous positive airway pressure is associated with significant biochemical improvement and reduction in NAFLD-related fibrosis.¹²⁴

Despite these associations between OSA and NAFLD, there are no guidelines for screening for OSA in the setting of NAFLD. A recent review by Mesarwi et al.,¹¹⁸ proposed screening patients with

NAFLD for OSA, because a large proportion of those with OSA are relatively asymptomatic. Further studies are required to assess the utility and cost-effectiveness for screening all patients with NAFLD for OSA. In general, behavioral modifications to promote weight loss are key, given the associated improvement in OSA severity and reduced upper airway collapsibility, and should be strongly recommended to patients with NAFLD and OSA.^{125,126}

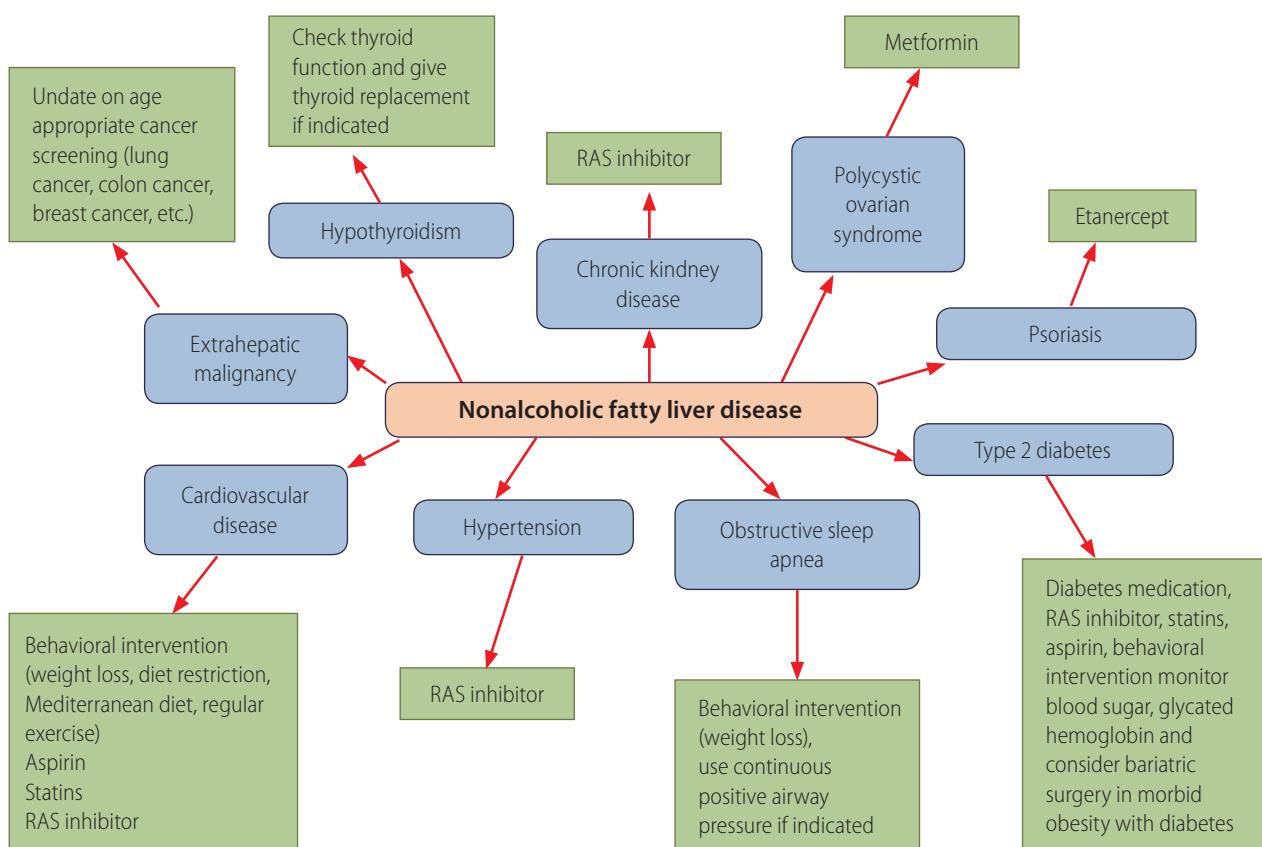
HYPOTHYROIDISM

Subclinical hypothyroidism or overt hypothyroidism is associated with an increased risk of NAFLD compared to euthyroid individuals.¹²⁷⁻¹³¹ Low thyroid function within euthyroid individuals was significantly associated with NASH and advanced fibrosis.^{128,132} A recent study based on the USA population-based study documented that low thyroid function was associated with a higher risk for overall and cardiovascular mortality in individuals with NAFLD.¹³³ The mechanism between hypothyroidism and NAFLD is thought to be related to increases in reactive oxygen species,

leptin hormone, and fibroblast growth factor-21, which lead to hepatic insulin resistance and NAFLD.^{130,131} Currently, resmetirom (MGL-3196), an orally active, liver-directed, selective thyroid hormone receptor-beta agonist, is a potential drug for the treatment of NASH and hyperlipidemia.^{134,135} A recent randomized, placebo-controlled phase 2 trial reported that resmetirom resulted in a significant reduction in hepatic fat content after 12 weeks and 36 weeks of treatment among patients with NASH.¹³⁶ Currently, there is insufficient evidence that screening hypothyroidism in individuals with NAFLD is cost-effective. However, physicians should be aware of the association between NAFLD and hypothyroidism because hypothyroidism is a modifiable risk factor. In a review by VanWagner and Rinella,¹⁰⁰ screening for thyroid dysfunction is recommended in patients with NASH.

POLYCYSTIC OVARIAN SYNDROME (PCOS)

PCOS is a common endocrinopathy in reproductive women that is associated with insulin resistance, elevated androgens, and



other metabolic comorbidities.¹³⁷ A recent meta-analysis showed that patients with PCOS had an approximately 3-fold higher risk of NAFLD independent of obesity status.¹³⁸ Hyperandrogenism was a risk factor for nonobese NAFLD independent of obesity, lipid profile, insulin resistance, or glycemic status, proposing a contribution of hyperandrogenism to nonobese NAFLD with PCOS.¹³⁹ In a retrospective study of reproductive age women with biopsy-proven NAFLD, PCOS was independently associated with more severe NASH, including advanced fibrosis.¹⁴⁰ The mechanism behind the association is likely related to insulin resistance, which is a hallmark feature of PCOS.¹⁴¹ Lifestyle modifications, including weight loss, increasing physical activity, and avoiding a high-fat diet, are the cornerstones of the initial treatment for both NAFLD and PCOS.¹⁴² Metformin can be used in patients with PCOS, but it has no role in the management of NAFLD. Currently, there are no studies that demonstrate a benefit of screening for PCOS in women with NAFLD, but hepatologists should ask their reproductive age women with NAFLD about irregular menses and hirsutism, given the potential implications of undiagnosed PCOS. Further studies are warranted to investigate potential treatment options for PCOS in those with NAFLD.

PSORIASIS

Several studies have shown an increased risk of NAFLD in patients with psoriasis or psoriatic arthritis.^{143,144} The exact mechanism for the association remains unclear, but it is postulated that inflammatory cytokines, such as tumor necrosis factor (TNF)- α , play a role in the association between NAFLD and psoriasis.¹⁴⁵ Moreover, the severity of psoriasis was also associated with an increased risk of NAFLD.^{143,144} In a systematic review and meta-analysis, NAFLD was associated with an increased risk for psoriasis after adjusting for comorbid risk factors.¹⁴⁶ A case series reported 89 patients with psoriasis, metabolic syndrome, and NAFLD who received etanercept (TNF- α inhibitor) compared with psoralen-ultraviolet A treatment; those who received etanercept had a significant reduction in aspartate aminotransferase/alanine transaminase ratio, fasting insulin, homeostasis model assessment index, and C-reactive protein level.¹⁴⁷ TNF- α inhibitors may be beneficial for psoriasis in patients with NAFLD, but larger cohort studies are warranted to confirm this finding.

CONCLUSION

NAFLD is a multisystemic disease that affects extrahepatic organ systems. Common extrahepatic manifestations in NAFLD include CVD, type 2 diabetes, metabolic syndrome, extrahepatic malignancies, CKD, hypothyroidism, PCOS, and psoriasis. Though the current guidelines do not provide guidance on the management of extrahepatic manifestation of NAFLD, the foundation of treatment for many of the extrahepatic manifestation associated with NAFLD remains lifestyle modification, including adequate weight loss, physical activity, and dietary modification (Fig. 1). Proposed screening strategies for common comorbidities in NAFLD include obtaining a fasting blood glucose, hemoglobin A1c, blood pressure, lipid profiles, estimated glomerular filtration rate, urine microalbumin and albumin creatinine ratio, and thyroid function tests; these may be considered in clinical practice to diagnose extrahepatic manifestations of NAFLD.¹⁰⁰ Physicians should also be aware that patients with NAFLD not only have an increased risk of hepatocellular carcinoma but of extrahepatic cancers as well. Therefore, patients with NAFLD should be kept up to date on cancer screening per current recommendations (Fig. 1). Further studies are needed to investigate the effect of pharmacologic treatment on extrahepatic manifestations of NAFLD.

Authors' contribution

Dr. Karn Wijarnpreecha was involved in study concept and design, acquisition of data, drafting of the manuscript, and critical revision of the manuscript. Dr. Elizabeth S. Aby was involved in study concept and design, acquisition of data, and drafting the manuscript. Dr. Ajaz Ahmed was involved in study concept and design, critical revision of the manuscript, and study supervision. Dr. Donghee Kim was involved in study concept and design, drafting of the manuscript, critical revision of the manuscript, and study supervision.

Conflicts of Interest

The authors have no conflicts to disclose.

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